Remarks:

Detailed Action

The Examiner states that Claim 35 is withdrawn from consideration as being drawn to nonelected species. However, Applicant does not see anywhere in the election/response office action received from the Examiner, nor in the Applicant's response to the election/restriction where the Applicant is requested to or does withdraw Claim 35. Therefore, Applicant respectfully requests that Claim 35 be returned to the claims listing for consideration. Claims 37 and 38 have been cancelled.

Rejection Under 35 U.S.C. §112

The Examiner has rejected Claims 1-34 and 36 under 35 U.S.C. § 112 first as not reasonably providing enablement for a method of isolating or visualizing a target cell from any embryonic stem cell as broadly claimed. The Examiner goes on to state that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Accordingly, the claims have been amended from "an embryonic stem cell" to "an embryonic stem cell of human, monkey or mouse."

The Examiner continues and on page 6 of the office action to state that the as filed specification is silent about isolation and visualization of any other species of ES cells other than mouse ES cells. The Examiner is directed to "Multilineage Differentiation from Human Embryonic Stem cell Lines," by Jon S. Odorico et al., published in *Stem Cells* 2001; 19;193-204 (attached hereto as a pdf entitled "Stem_Cells"). This article sets out the differentiation of human ES cells. Furthermore, differentiation of monkey ES cells is described in "Isolation of a primate embryonic stem cell line," Proc. Natl, Acad. Sci.USA, Vol. 92, pp. 7844-7848 (attached hereto as pdf "Primate_Stem _cells").

Finally in response to the §112 rejection of the phrase "a selective marker gene," said phrase has been replaced by "a fluorescence protein gene" in order to clarify the claims.

Rejection Under 35 U.S.C. §103

The Application was rejected under 35 U.S.C. § 103 as being unpatentable under Vallier et al, (PNAS, 2001, 98:2467-2472) (hereinafter "Vallier") in view of Ong et al., US Patent No. 6,777,235, (hereinafter "Ong") and further in view of Rybkin et al., (Biol. Chem., 15927-15934, 2003) (hereinafter "Rybkin"). First it must be noted that the references cited fail to disclose, and neither describe or suggest, how to solve a great problem solved by the present invention. That is, the problem that activity (expression intensity) of a tissue-specific promoter is too low for isolation or visualization of target cells from an embryonic stem cell.

Claims 1-13, 24-33 have been amended (and remaining claims depend therefrom) to include the phrase "in vitro" as it is obvious from the "best mode for carrying out the invention" in the specification that the present invention is the method concerning in vitro differentiation of ES cells.

With respect to Vallier et al, although the reference shows an increase in the number of positive cells of EGFP (at Table 1), there is neither description nor suggestion about elevating the expression intensity of EGFP, as is disclosed in the present invention.

Also, Rybkin the Cre system is not used for in vitro differentiation of ES cells, but rather it is used for producing a transgenic mouse. This is an in vivo usage of the Cre system. In other words, in Rybkin the Nkx2.5 acts on the embryologic stage in the fetus of the mouse. Alternatively, in the present invention, Nkx2.5 acts on in vitro differentiation of ES cells. This is entirely different.

Further, in Rybkin and Ong, the DNA of interest is integrated to target cells. However, the work to achieve strain by integration requires an excessive amount of time and is also extremely labor intensive. Moreover, if integration of DNA of interest is used for in vitro differentiation of ES cells, it is well known that the structure of chromosome is influenced and the expression of gene is unstable and shut off.

On the other hand, the present invention is not integrated by introducing arbitrary promoter into Cre-expressing adenovirus. Therefore, in the present invention the labor and time needed are remarkably reduced for producing the Cre expression adenovirus which this promoter is introduced into. Moreover, in the present invention, since the introduced gene of interest is maintained in the cell nucleus under episomal conditions, this gene is stable and the expression of this gene is not influenced by the host's chromosome.

Finally, in Yamamoto, the Cre-expressing adenovirus are used for in vivo. However, the present invention is used for in vitro. The Cre-expressing adenovirus of the present invention also differ from those disclosed in Yamamoto.

Therefore, as set out above, the present invention would not have been motivated by the references cited.

Conclusion:

Applicant believes that this communication is intended to be fully responsive to the outstanding Office Action and fully addresses the Examiner's rejections and now places the application in condition for allowance. No new matter has been added.

Please charge any fee deficiency or credit any overpayment with respect to this paper and or this application to Apex Juris Deposit Account No. 50-2069. Should Examiner believe further discussion regarding the above claimed language would expedite prosecution they are invited to contact the undersigned at the number listed below.

In view of the above, Applicant respectfully submits that each of claims 1 through 36 recites statutory subject matter that is novel and new, is subject matter of the present invention and is fully supported in the disclosure of the present invention, and therefore respectfully requests that claims 1 through 36 be found allowable and that this application be passed to issue. No new matter has been included.

If for any reason, the Examiner determines that the application is not now in condition for allowance, it is respectfully requested that the Examiner contact the Applicant's

undersigned attorney at the indicated telephone number to arrange for an interview to expedite the disposition of this application.

In the event this paper has not been timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to counsel's Deposit Account No. 50-2069, **referencing docket number 042-301**.

Respectfully submitted,

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